REMARKS/ARGUMENTS

A. Sequence Compliance

At page 6 of the office action, the Examiner alleges that Figure 2j contains nucleotide sequences without a sequence identifier. In response, Applicants submit a substitute sheet for Figure 2j in which the sequence is properly identified with the sequence identifier SEQ ID NO: 6.

B. Objections to Drawings

At page 7 of the specification, the Examiner objected to Figure 17 because the specification does not separately describe Figure 17A and Figure 17B. In response, Applicants amend the specification by submitting an amendment to the specification in which applicants add reference characters A and B in the description of Figure 17.

C. Objections to the Specification

At page 7 of the specification, the Examiner objected to applicants' paragraph [0094] because the paragraph contains an embedded hyperlink and requested that applicants delete the link. In response, applicants submit a replacement paragraph in which the link is deleted.

At page 7 of the office action, the Examiner objected to applicants' use of trademarks POLYFECT™ reagent and SUPERFECT™ reagent because the marks are not capitalized and are not accompanied by generic terminology. In response applicants submit a replacement paragraph in which the trademarks are capitalized. As to the generic terminology for the trademarks, the MPEP provides that "if the trademark has a fixed and definite meaning, it constitutes sufficient identification unless some physical or chemical characteristic of the article or material is involved in the invention." MPEP § 608.01.

Applicants respectfully submit that no physical or chemical characteristics of the POLYFECT™ or SUPERFECT™ reagents are involved in the invention. Rather, as stated in paragraph [0137] of the specification, Applicants' vectors can be delivered to the target cells via standard gene delivery methods. Applicants then provide examples of such methods such as lipid mediated transfection, activated dendrimers (POLYFECT™ or SUPERFECT™ reagents from Qiagen), phenylethyleneimide (PEI), receptor mediated transfection . . . etc.

Thus, because no physical or chemical characteristics of the regents are involved in the invention, Applicants believe that in agreement with the above-cited MPEP § 608.01, applicants

do not have to provide additional generic terminology for the marks beyond defining them as activated dendrimers.

D. Objections to the Claims Should be Withdrawn

At page 8 of the office action, the Examiner objected to claim 1 because of the following formalities: the numbering of elements is not consistent with steps in the claim. In response, Applicants amend claim 1 so that the numbering of elements is now consistent with the steps. The steps are now listed as A, B and C.

At page 8 of the office action, the Examiner objected to claims 3 and 4 for the same reasons as applied to claim 1. In response, Applicants amend claims 3 and 4 by listing step "vi" as step B.

At page 8 of the office action, the Examiner objected to claim 2 because the numbering of elements in the claim is not consistent with the number of steps. In response, Applicants amend the claim by listing steps as A, B, C and D.

At page 8 of the office action, the Examiner objected to claims 5 and 6 for the same reasons as applied to claim 2. In response, Applicants amend claims 5 and 6 by referring to step vi as step B.

At page 8 of the office action, the Examiner objected to claim 21 and suggested that the last word in the claim is replaced with the word "vector." In response, Applicants amend claim 21 by replacing the last word of the claim with the word "vector."

At page 9 of the office action, the Examiner objected to claim 22 because the scope of the claim is broader than that of independent claims from claim 22 depends. In response, Applicants cancel claim 22.

At page 9 of the office action, the Examiner objected to claim 23 because of alleged improper dependency from claim 8. In response, Applicants cancel claim 23.

At page 9 of the office action, the Examiner objected to claims 29 and 30 because the claims should refer to other claims in the alternative only. In response, Applicants amend the claim 29 so that the claim now depends only from claim 1. In response, Applicants also amend the claim 30 so that the claim now depends from claims 1 or 2 in the alternative.

At page 10, the Examine objected to claims 31 and 32 because the claims improperly depend from a multiple-dependent claim. In response, Applicants limit the dependency of

claims 31 and 32 to claim 29 only. Applicants also introduce new claims 33 and 34 that depend on claim 30 only. Claims 33 and 34 do not introduce any new matter and simply recapture dependency from claim 30 that had to be deleted from claims 31 and 32.

In conclusion, Applicants have amended claims 1, 2, 3, 4, 5, 6, 21, 22, 23, 29, 30, 31 and 32 to overcome Examiner's objections as stated above. Therefore, the Examiner may properly withdraw the objections.

E. Double Patenting Rejections Should be Withdrawn

At page 11 of the Office action the Examiner issued a provisional double patenting rejection for Applicants' instant claims over clams of applicants' copending patent application 10/810,976. The Examiner then requested that Applicants file a terminal disclaimer to overcome this provisional obviousness-type double-patenting rejection.

A provisional obviousness double-patenting rejection is a subject to the issuance of the conflicting claims. Specifically, the MPEP provides:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

MPEP. § 804 (I) (B) (1)

The present patent application was filed September 12, 2003. Co-pending 10/810,976 was filed on March 26, 2004. Thus, the present patent application is the earlier filed of the two pending applications. Consequently, if Applicants overcome all other rejections with this response, the above-identified application may be allowed without a terminal disclaimer.

F. Claim Rejections under 35 USC §112 Should be Withdrawn

At page 12 of the office action, the Examiner rejected claims 1, 3, 4, 7, 8, 11-23 and 26-28 under 35 UCS §112, second paragraph. The Examiner alleges that the claims are indefinite for failure to particularly point and distinctly claim the subject matter which Applicants regard as their invention.

With respect to claim 1, the Examiner alleged that the claim is vague and indefinite the metes and bounds of the phrase "inserted at a random position within two exons" are not clear. In response Applicants amend claim 1 by replacing "within" with "between."

In addition to claim 1, the Examiner also rejected claims 3, 4, 7, 8, 11-23 and 26-28 that depend from claim 1 for the same reasons as those applied to claim 1. Because Applicants amend claim 1 with this response, the Examiner may properly withdraw the rejections of claims 3, 4, 7, 8, 11-23 and 26-28.

With respect to claim 7, the Examiner alleges at page 13 of the office action that the claim is vague and indefinite because of applicants' use of the term "SAVI method." In response, applicants cancel claim 7.

With respect to claim 27, the Examiner rejected the claim at page 13 of the office action because the limitation "the oligonucleotide having a specific sequence" in line 2 of the claim. In response, Applicants amend the claim by reciting the limitation to ". . . the polynucleotide construct [that] further comprises, downstream of the oligonucleotide **sequence encoding an assayable marker** ~~**having a specified sequence,**~~ a sequence encoding, upon expression, a selectable marker."

At page 14 of the Office action, the Examiner rejected claim 22 under 35 U.S.C. §112, first paragraph, and requested that vector pGT-fs0 be deposited with the American Tissue Collection bank. Applicants submit that the rejection is moot in view of the cancellation of claim 22.

In conclusion, in light of the above amendments to the claims, Applicants submit that rejection of claims 1, 3, 4, 7, 8, 11-23 and 26-28 under 35 U.S.C. §112, second paragraph may be properly withdrawn.

G. Claim Rejections under 35 USC §103 Should be Withdrawn

1. Rejection over Jarvik in view of Smith as evidenced by New England Biolab Catalog.

At page 15 of the Office action, the Examiner rejected claims 1, 12 and 17-21 under 35 U.S.C. §103(a) as being unpatentable over US patent 5,652,128 to inventor Jarvik (Jarvik) in view of Smith (BioTechniques, Vol. 23, No.1, pages 116-120, 1997) as evidenced by 1996 New England Biolab catalog, page 39.

Claim 1 of the instant application recites a method for elucidating a protein expression profile of a test cell line or group of cells, the method comprising:

A) randomly introducing into the genome of a cell or group of cells a promoterless polynucleotide construct, the construct comprising in a 5' to 3' orientation:

i) a splice acceptor consensus sequence;

ii) a complementary sequence of a first type IIS restriction enzyme recognition sequence;

iii) an oligonucleotide sequence encoding an assayable marker peptide;

iv) a sequence of a second type IIS restriction enzyme recognition sequence;

v) a splice donor consensus sequence;

wherein said promoterless polynucleotide construct when introduced into an actively expressed gene results in the generation of a fusion protein, containing the assayable marker peptide inserted at a random position between two exons coding for the cellular protein encoded by said gene;

B) identifying those cells expressing said marker peptide fused to said cellular protein; and

C) determining the identity of the proteins to which the marker peptide is fused in each group of cells.

Thus, the claim recites methods in which the protein expression profile of cells is elucidated in a way that allows the high-throughput and simultaneous analysis of the protein and RNA expression profiles of multiple gene trapping events taking place in multiple clones present in a subpopulation of cells sorted according to the level of expression of the reporter gene, without the need of performing sequence analysis on isolated individual clones.

The Examiner characterized Jarvik as disclosing a method of tagging genes and proteins, comprising the steps of (1) randomly introducing a CD-DNA construct by nonhomologous recombination into the genome of eukaryotic cells, (2) identifying those cells that express the CD tagged protein and (3) determining the sequence identity of the protein or nucleic acid to which the CD tag has been fused (e.g. column 8, lines 20 to column 9, line 61; column 4, lines 9-20). The Examiner further stated that Jarvik discloses the CD-DNA construct containing a splice acceptor and a splice donor flanking a peptide-encoding segment (e.g. Figure 2).

The Examiner then characterized Smith as disclosing an mini-exon comprising in a 5' to 3' orientation 1) a splice acceptor consensus (3'CS); 2) the sequence complementary to MnlI type IIS restriction enzyme recognition sequence; 3) an oligonucleotide encoding a myc epitope that does not provide the initiation codon and lacks a stop codon; 4) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence; and 4) a splice donor.

Applicants bring to the Examiner's attention that Figure 1 of Smith clearly shows that the exon described by Smith (defined by nucleotides 28-157) contains six Mnl I restriction sites at nucleotide positions 55-58, 63-66, 95-98, 103-106, 135-138 and 143-146. The MnlI recognition and cleavage positions for all six MnlI restriction sites are located within the Smith exon and NOT at the borders of the myc exon. Because there are six type IIS restriction enzyme recognition and cleavage sequences in the Smith construct and because the sequences are located inside the myc exon, restriction of the Smith construct with a type IIS restriction enzyme cuts the myc exon into pieces and destroys the marker so that the Smith marker cannot be assayed after the restriction. In contrast to the Smith construct, an assayable marker of the instant construct is intact after restriction with a type IIS restriction enzyme and can be detected by assays as described in the instant specification.

To summarize, the location and orientation of MnlI restriction sites in the Smith construct do not allow obtaining information (by SAVI or by any other method) about the nucleotide sequence derived from cellular exons fused to the exon during RNA splicing, while the instant methods permit obtaining such information. Thus, the Smith construct cannot be used to identify the exons that are fused to the myc epitope and does not render the instant claims obvious.

Neither Jarvik nor Smith discloses or suggests a method of elucidating a protein expression profile. Instead both, Jarvik and Smith are concerned with identifying new genes (see abstracts of Jarvik and Smith). The references disclose constructs that differ from that recited in instant claim 1.

As stated above, claim 1 discloses a construct in which restriction recognition sites flank the assayable marker, while neither the Jarvik nor Smith constructs include an assayable marker which is flanked with RE IIS sequences. The Examiner concedes that Jarvik does not disclose such elements at all. The Smith construct contains the restriction sites inside the Smith marker.

Jarvik is further different from Applicants's invention in that that Jarvik does not provide a method to retrieve sequence information from the tagged proteins, does not disclose flanking

Type IIS restriction sites at the 5' and 3' ends of the inserted exon and does not describe the method of SAVI to retrieve sequence tags. Jarvik does not identify the genomic site of integration or the identity of the gene to which the reporter is fused to.

The miniexon described by Jarvik does not contain Type IIS restriction sites in the proper orientation to capture upstream and downstream sequence tags that reveal the identity of the cellular exon directly fused to the reporter exon. Jarvik would need cloning of individual cells showing expression of the reporter protein and performing a separate analysis of the protein tagged and gene integration site for each clone. Applicants' method allows the simultaneous identification of integration sites from multiple mixed clones. Jarvik does not classify the population of gene trapped cells in subpopulations of cells based on the level of expression of the reporter gene. Jarvik et al. cannot simultaneously characterize multiple trapped genes and assign a defined level of gene expression to those genes. Applicants' method classifies the population of cells in separate subpopulations based on the level of expression, followed by analysis of all sequence tags present in each subpopulation in order to identify the individual events of gene trapping present in each and one of the separated subpopulations, which allows to reconstruct the "distribution profile of protein expression" or "protein expression profile" for each protein fusion present in different subclones within a mixed population of clones. The Jarvik approach requires a clonal analysis to identify these particular events. Applicants' approach identifies this heterogeneity in gene expression between cells belonging to a particular clone, without the need of clonal analysis.

In conclusion, the Jarvik/Smith combination does not disclose or suggest instant methods recited by claims 1, 12 and 17-21. Furthermore, neither of the references discloses the construct used in applicants' methods. Consequently, the combination does disclose or suggest each of the elements recited by claims 1, 12, and 17-21 and rejection of the claims under 35 USC §103 may be properly withdrawn and such withdrawal is herein requested.

2. Rejection over Jarvik in view of Smith and further in view of Morin

At page 18 of the office action, the Examiner rejected claims 1, 12, 14, 15 and 17-21 under 35 USC §103 over Jarvik in view of Smith and further in view of Morin. The Examiner once again repeated that Jarvik discloses a construct comprising splice acceptor and donor sites and that Smith discloses a mini-exon construct comprising RE IIS recognition sites. As

discussed above, the Smith construct is significantly different from that recited in the methods of the instant invention because RE IIS recognition and cleavage sites in the Smith construct are located inside the assayable marker and restriction of the Smith construct with the corresponding restriction endonuclease results in disruption of the Smith marker, while restriction with the corresponding endonuclease of a marker recited by the instant claims does not result in disruption of the marker.

At page 19 of the office action, the Examiner characterized Morin as teaching a mini-exon comprising EGFP. In fact, Morin discloses a P-element construct to be used in drosophila cells for cloning new genes from such cells (see abstract of Morin).

Morin et al describe a method to detect the subcellular localization of proteins by gene trapping and tagging with GFP as the marker exon and recovery of the transposon insertion points by inverse PCR from genomic DNA. The paper of Morin is an example of random insertion of transposons encoding a reporter gene (GFP) in insect cells. This system does not have elements in common with Applicants' method. The Morin transposon does not incorporate type IIS restriction sites at the borders of the exon to allow the recovery of sequence tags corresponding to exons fused to the GFP exon by RNA splicing. Morin et al determines transposon insertion points by inverse PCR from genomic DNA, not from RT-inverse PCR. The vectors of Applicants' invention incorporate an additional and original element, a Type IIS restriction site at the exon borders to allow the high-throughput characterization of exon sequence tags fused by splicing to the reporter exon. Morin et al require the derivation of cloned lines carrying isolated insertions and separate analysis of each of the insect lines. The technique does not involve separating the gene trapped cells in subpopulations according to the level of expression of the gene trapped protein. Morin does not quantify the level of expression of the fusion protein. Morin cannot simultaneously characterize multiple trapped genes and assign a defined level of gene expression to those genes.

The rejected claims are directed to methods of elucidating protein profile in a cell or in a group of cells, which is not taught or suggested by the cited references.

As discussed above, neither Jarvik, nor Smith discloses or suggests a method of identifying a protein profile in a cell or in a group of the cells. Morin does not disclose or suggest such a method either. Further, neither Jarvik nor Smith discloses or suggests a construct recited by the rejected claims. The Morin construct does not include the recited elements either

because the Morin construct is a P-element construct applicable for integration into drosophila cells that does not comprise RE IIS sites flanking an assayable marker.

In conclusion the Jarvik/Smith/Morin combination does not teach or suggest methods of the rejected claims, therefore the rejection of claims 1, 12, 14, 15, and 17-21 under 35 USC §103 can be properly withdrawn and this withdrawal is respectfully requested.

3. Rejection over Jarvik in view of Smith further in view of Morin and Sinclair

At page 20 of the office action, the Examiner rejected claims 1, 12, 14-21, 26 and 27 under 35 USC §103 over Jarvik in view of Smith further in view of Morin and Sinclair.

The shortcomings of the Jarvik/Smith/Morin are discussed above. The combination does not disclose or suggest the instant methods and does not disclose or suggest a construct recited in the instant methods. The Examiner cited Sinclair because Sinclair discloses a GFP protein that is optimized for expression in human cells. However, the toxicity of Aquorea GFP was not described in any of those references. Moreover, transgenic mice encoding Aquorea GFP have been created and no signs of toxicity have been reported in these mice. See FEBS Lett. 1997 May 5; 407(3):313-9.

The rejected claims are concerned with elucidating a protein profile in a cell or in a group of cells. Sinclair does not disclose or suggest any methods for elucidating protein profiles. Sinclair does not disclose or suggest a construct recited in the rejected method claims. In conclusion, Sinclair does not remedy deficiency of Jarvik/Smith/Morin which do not teach any methods or elucidating protein profile in a cell or in a group of cells or disclose or suggest a construct recited in the rejected method claims.

In conclusion, because the Jarvik/Smith/Morin/Sinclair combination does not disclose or suggest the methods claimed in claims 1, 12, 14-21, 26 and 27 or a construct recited in the claims, the rejection of the claims under 35USC §103 over the combination can be withdrawn and this withdrawal is respectfully requested.

4. Rejection over Jarvik in view of Smith and Keeton

At page 23 of the office action, the Examiner rejected claims 1, 2, 12 and 17-21 under 35 USC §103 over Jarvik in view of Smith and Keeton.

At page 25 the Examiner characterized Keeton as teaching that scientists cannot rely upon a guess and must use a system of standards based upon mathematical possibility.

Applicants want to point out that Jarvik does not disclose or suggest specific methods identifying a CD-tagged protein. The method proposed by Jarvik to investigate the effect of a drug or hormone on the expression of a tagged protein could potentially be applied only to an isolated clone that contains a single tagged protein per genome. Only under those circumstances, a person skilled in the art could compare the effect of a drug or hormone on the protein expression of that single tagged protein by comparing the effects of the drug on treated and non treated cells derived from the same clone by using the Jarvik method. Therefore, the method of Jarvik involves the steps of a) introducing a CD-tagging exon into a population of cells, b) isolating individual clones (not based on epitope detection with an antibody since that would be destructive to the cell), c) determine the identity of the protein tagged (by undisclosed methods), d) treating the cell clone with a drug and e) testing the effects of the drug on the expression of the tagged protein.

In contrast, the method of the instant invention allows testing the effect of a drug on multiple genes at the same time by sorting cells into subpopulations of cells according to the levels of expression of the tagged proteins, and then analyzing the identity of the genes and comparing the level of expression of multiple genes derived from a population of treated cells with the level of expression of multiple genes derived from the population of non-treated cells.

As discussed above, the method of Smith does not suggest the use of Type IIS restriction enzymes at the border of the tagging exon to determine the identity of the exons flanking the tagging exon and therefore, combination of the teachings of Jarvik with the teachings of Smith do not fulfill the goal, method steps or vector structures of the instant application.

The Examiner further combines the teachings of Jarvik and Smith with the teachings of Keeton to justify obviousness of the present invention. Claim 1 does not rely on statistical comparison of two populations of cells and therefore it should not be obvious based on Jarvik in view of Smith and in view of Keeton. Claim 2 requires that two protein expression profiles obtained for two populations of cells by the method of the present invention are compared in order to determine the differentially expressed proteins. Claim 2 has been amended to recite:

Claim 2: .....viii) comparing ~~by statistical methods~~ the protein expression profiles....

Amended Claim 2 does not refer to statistical methods and therefore cannot be obvious in view of Keeton.

In conclusion, the Jarvik/Smith/Keeton combination does not disclose or suggest a method for elucidating a protein profile in a cell. The combination does not disclose or suggest a construct recited in claims 1, 2, 12 and 17-21. Therefore, the rejection of claims 1, 2, 12 and 17-21 under 35 USC §103 may be properly withdrawn and this withdrawal is respectfully requested.

5. Rejection over Jarvik in view of Smith, Keeton and Whitney

At page 26 of the office action, the Examiner rejected claims 1, 2-6, 12, 13, 17-21 and 28 under 35 USC §103 over Jarvik in view of Smith, Keeton and Whitney.

The rejected claims recite methods for elucidating protein profile in a cell or in a group of cells. The claims recite a construct in which RE IIS cites flank an assayable marker. As explained above, Jarvik, Smith and Keeton do not disclose or suggest the methods or the construct.

At page 28 of the office action, the Examiner characterized Whitney as disclosing a method for testing compounds useful in regulating gene expression.

Whitney does not disclose or suggest a method for elucidating a protein profile in a cell or in a group of cells. Whitney discloses the production of a library of clones generated by gene trapping with the beta-lactamase (BL) protein as the tagging exon, incubating such population of cells with a FRET-based BL fluorescent substrate, and separating the population of cells into two pools by FACS based on the color of the cells, which is indicative of the presence or absence of BL activity in each individual cell. The method is designed to detect changes in protein expression induced by treatment of any of the two populations with a drug or hormone. Therefore, the method of Whitney allows the comparison of the same population of cells before and after the treatment of the cells with a drug or other stimulus. Cells that change color after treatment with the drug are indicative of tagged genes whose expression was induced or repressed by the stimulus. Isolation of such cells by FACS and subsequent identification of the gene trapping events by 5'RACE allows determination of the genes whose expression is affected by the drug treatment. The method of Whitney requires some "transition" or transformation of the expression profile of the same population of cells. On the contrary, the method of the present

invention allows the comparison of two separate populations of cells, either obtained before or after the treatment with a drug or two populations of complete different origins. For example, the method of the present invention allows the comparison of expression profiles of normal cells with cancer cells of the same or different tissue type, a comparison that cannot be performed by the method of Whitney, since it is not possible to induce the transition of a tumor population of cells to a normal non-transformed phenotype or vice versa upon a stimulus.

Furthermore, the invention disclosed by Whitney describes a method that investigates which portion of the proteome responds or is directly or indirectly associated with a biological response. On the contrary, Applicant's method describes the whole tagged proteome and does not require association to any biological response. Also, Whitney's method does not allow separation of cells based on different levels of expression of the fusion proteins, except for separation between cells showing changes (ON/OFF) in protein expression levels upon a stimulus. Moreover, the method of Whitney requires the comparison of two populations before and after a stimulus to determine the portion of the proteome that suffers a change upon stimulus. Instead, the method of the present invention allows the characterization of the whole protein expression profile of a single cell population without the need to subject this population to a stimulus.

In summary, Whitney does not disclose or suggest a construct comprising RE IIS recognition sites that flank an assayable marker. Consequently, Whitney does not remedy the shortcomings of the other references in the Jarvik/Smith/Keeton/Whitney combination.

In conclusion the Jarvik/Smith/Keeton/Whitney combination does not disclose or suggest methods or constructs recited by claims 1, 2-6, 12, 13, 17-21 and 28. Therefore, rejection of the claims under 35 USC 103 over the Jarvik/Smith/Keeton/Whitney combination may be properly withdrawn and such withdrawal is herein requested.

6. Rejection over Hopkins in view of Smith.

At page 30 of the office action, the Examiner rejected claims 1, 11, 12 and 17-21 under 35 USC §103 over Hopkins in view of Smith.

At page 30 of the office action, the Examiner characterized Hopkins as a method for determining gene expression comprising contacting a cell with a retrovirus, identifying cells that integrated the retrovirus and cloning a gene into which the retrovirus has integrated.

The rejected claims are method claims for elucidating a protein profile in a cell or in a group of cells. The Hopkins methods are methods for introducing mutations into the genes (abstract, Figures 1 and 2). Hopkins does not disclose a construct recited by the instant claims and in which there are two RE IIS recognition sites flanking an assayable marker. Hopkins does not disclose or suggest a method for elucidating a protein profile in a cell or in a group of cells.

Hopkins et al. uses gene trapping retroviruses to introduce mutations in the germline of living organisms. Hopkins et al. describes a classic retroviral vector carrying a gene trapping cassette consisting in a branch point sequence, a polypyrimidine tract, a splice acceptor and donor sequences flanking an artificial exon that encodes a reporter protein. After the mutagenesis experiment, Hopkins et al. characterize the identity of the truncated gene by 5'RACE. The vectors of the present invention incorporate an original element, Type IIS restriction site at the exon borders to allow the high-throughput characterization of exon sequence tags and two non-type IIS restriction sites which allow for recovery of the sequence ditags and concatenation of ditags into a high order polymer to facilitate the high throughput determination of sequence tags. The method described by Hopkins does not involve separating the gene trapped cells in subpopulations according to the level of expression of the gene trapped protein but instead they quantify the level of expression of the gene trapped expression unit by quantitative PCR, starting from isolated cloned cells. Furthermore, Hopkins et al do not quantify the level of expression of the fusion protein and cannot simultaneously characterize multiple trapped genes and assign a defined level of gene expression to those genes.

To summarize, Smith does not disclose a construct in which two RE IIS recognition sites are flanking an assayable marker. Instead Smith discloses a construct in which the sites are located inside the marker. Thus, the Hopkins/Smith combination does not disclose or suggest methods for elucidation a protein expression profile in a cell or in a group of cells. The combination does not disclose or suggest a construct recited by claims 1, 11, 12 and 17-21. Consequently, rejection of claims 1, 11, 12 and 17-21 under 35 USC §103 over the Hopkins/Smith combination can be properly withdrawn and this withdrawal is herein respectfully requested.

CONCLUSION

Applicants believe that the application is in good and proper order for allowance and such allowance is respectfully solicited. The Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below with any questions, comments or suggestions relating to this application. Should any additional fees be required for further prosecution of the above-identified patent application, the Commissioner is authorized to deduct any such fees from Howrey LLP Deposit Account No. 08-3038, referencing the above-identified docket number.

Respectfully submitted,

HOWREY LLP

Dated: May 1, 2007

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